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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/577,005	ASAKURA ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-11,13 and 15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-19 are pending.

The request filed on 10/9/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/577005 is acceptable and a CPA has been established. An action on the CPA follows.

It is noted that since no amendment to the claims was filed with the request for a CPA, elected claims 14 and 12 have been examined as originally filed and as amended in a preliminary amendment in Paper No. 3, filed on 5/25/2000, respectively.

This application contains claim 1-11, 13 and 15-19 drawn to an invention nonelected with traverse in Paper No. 9, filed on 10/10/2001. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

1. The abstract of the disclosure is objected to because of grammatical errors and use of improper idiomatic English. For example, "method of producing coryneform bacteria having an improved amino acid- or nucleic acid-productivity comprises the steps of " instead of "method of producing coryneform bacteria having improved amino acid or nucleic acid productivity comprising the steps of", "this method can construct a mutant capable" instead of "this method allows the construction of a mutant capable", etc. Correction is required. See MPEP § 608.01(b).

3. The disclosure is objected to under 37 CFR 1.71 because of grammatical/typographical errors and use of improper idiomatic English. For example, "enzumes" in page 6, line 18, "mutagtenesis" in page 2, line 28, "prompter" in line 11, page 9 of the specification, "specifrrfically" in line 20, page 11 of the specification, etc. Correction is required. Applicant should be careful not to introduce any new matter into the disclosure (i.e., matter which is not supported by the disclosure as originally filed).

Priority

2. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to PCT/JP99/05175 filed on 09/22/1999, JAPAN application 271786/1998 filed on 09/25/1998 and JAPAN application 271787/1998 filed on 09/25/1998.

Information Disclosure Statement

3. The submission of an information disclosure statement (IDS) in Paper No. 4, filed on 7/17/2000 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement was considered by the Examiner and a copy of the PTO 1449 was forwarded to Applicants in Paper No. 10, mailed on 12/14/01. The Examiner inadvertently omitted to initial references AA and AB. A copy of the PTO 1449 submitted on 7/17/2000 is being forwarded to Applicants with this Office Action.

4. The submission in Paper No. 5, filed on 9/7/2000, of a list of Applicant's pending applications which may be related to the examination of the instant application is acknowledged.

5. The submission in Paper No. 6, filed on 10/31/2000, of a list of Applicant's pending applications which may be related to the examination of the instant application is acknowledged.

6. The submission in Paper No. 7, filed on 1/26/2001, of a list of Applicant's pending applications which may be related to the examination of the instant application is acknowledged.

7. The submission in Paper No. 11, filed on 12/14/2001, of a list of Applicant's pending applications which may be related to the examination of the instant application is acknowledged.

Drawings

8. As indicated in previous Office Action Paper No. 10, the drawings were reviewed and were approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Objections

9. Claim 12 is objected to as being dependent upon non-elected claim 4. For examination purposes, the limitations recited in claim 4 will be incorporated in the interpretation of claim,12. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 12 (claim 14 dependent thereon) is indefinite in the recitation of "gene having a promoter according to Claim 4" because claim 4 is directed to a method and not to a promoter. For examination purposes, only the portion of claim 4 which refers to a promoter will be considered. It is suggested that the portion of claim 4 directed to the promoter be incorporated in claim 12. Correction is required.

13. Claim 12 (claim 14 dependent thereon) is indefinite in the recitation of "glutamic acid-synthesizing gene" as it is unclear what the meaning of the term is. As known in the art, many enzymes are involved in the biosynthesis of glutamic acid, each encoded by different genes. Therefore, it is unclear if the intended meaning is any gene which encodes any of the enzymes involved in glutamic acid synthesis or a specific gene which encode one enzyme involved in biosynthesis of glutamic acid. For examination purposes, it will be assumed that the term "glutamic acid-synthesizing gene" is equivalent to "any gene encoding any enzyme involved in the biosynthesis of glutamic acid". Correction is required.

14. Claim 12 (claim 14 dependent thereon) is indefinite in the recitation of "the glutamate dehydrogenase (GDH) gene" since there is no antecedent basis for such gene. Correction is required.

15. Claim 12 (claim 14 dependent thereon) is indefinite in the recitation in claim 4 of "promoter for glutamate dehydrogenase (GDH) gene has a DNA sequence selected from the group consisting of .....CGGTCA, TTGTCA, TTGACA, and TTGCCA " for the following reasons. Claim 12 ultimately refers to claim 1 in regard to the promoter recited. Since claim 1 refers to a promoter which is mutated, it is unclear if the promoter comprising the hexamers recited in claim 4 is the promoter before mutations have been introduced or after mutations have

been introduced. For examination purposes, it will be assumed that the promoter comprising the hexamers recited in claim 4 is the mutated promoter. Furthermore, the term "has a DNA sequence selected..." implies that the promoter's complete DNA sequence is any of the hexamers recited, which is unclear since promoters usually have more than 6 nucleotides. If the intended meaning of the term is "comprising a DNA sequence selected from the group consisting of", the claim should be amended accordingly. Correction is required.

16. Claim 12 (claim 14 dependent thereon) is indefinite in the recitation in claim 4 of "the promoter for glutamate dehydrogenase (GDH) gene has a DNA sequence selected from the group consisting of (i) at least one DNA sequence" in claim 4 because it is unclear and confusing. As written, one cannot clearly establish which DNA sequence is in item (i) or which is the relationship between said sequences and the –35 consensus region. It appears that the items recited are in a multiple alternative format. Correction is required.

10. Claim 12 (claim 14 dependent thereon) is indefinite in the recitation of "TATAAT sequence or the same TATAAT sequence but in which the base of ATAAT is replaced with another base in –10 region" as it is confusing language. It is not clear which base is being referred to and what the relationship between the sequence and the –10 region is. Correction is required.

11. Claim 12 (claim 14 dependent thereon) is indefinite in the recitation of "(iii) a combination of (i) and (ii), wherein the sequence does not inhibit the function of the promoter" for the following reasons. First, it is unclear what combination is being referred to absent clarification of what is claimed in (i) and (ii). Second, it is not clear which sequence should not inhibit the function of the promoter. Correction is required.

17. It is noted that for examination purposes, claim 12 will be interpreted as being drawn to any gene encoding any enzyme involved in the biosynthesis of glutamic acid wherein said gene is linked to a promoter comprising any of the following hexamers: CGGTCA, TTGTCA, TTGACA, TTGCCA, or TATAAT. It is suggested that if Applicant's intended limitations are related to the -35 and -10 consensus regions, the claim be amended to clearly establish which hexamers can be in the -35 consensus region and which hexamers can be in the -10 consensus region.

Claim Rejections - 35 USC § 112, First Paragraph

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. Claims 12 and 14 are drawn to a genus of genes from any organism encoding genera of enzymes involved in the biosynthesis of glutamic acid wherein said genes are linked to genera of promoters comprising any of the hexamers as indicated above or to a genus of coryneform bacteria comprising said genus of genes. See claim rejections under 35 USC 112, second paragraph above for claim interpretation. While the specification discloses the production of coryneform bacteria having mutant promoters for the coryneform bacteria glutamate

dehydrogenase, citrate synthase, isocitrate dehydrogenase, pyruvate dehydrogenase and arginosuccinate dehydrogenase genes, there is no disclosure of (1) other genes involved in the biosynthesis of glutamic acid from other organisms, (2) the promoters of other genes involved in the biosynthesis of glutamic acid from other organisms comprising the recited hexamers, or (3) the critical structural elements a polypeptide should have to display the desired enzymatic function.

While one could argue that the claimed genus of genes is adequately described since one can isolate genes from other organisms encoding proteins of similar function by sequence comparison using the polypeptide structures disclosed in the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a few species which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all

species within the claimed genus. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

21. Claims 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a coryneform bacterium glutamate dehydrogenase gene linked to a mutated coryneform bacterium promoter comprising the hexamers as recited in the claim (see claim interpretation above for list of hexamers), does not reasonably provide enablement for any gene from any organism encoding any enzyme involved in glutamic acid biosynthesis wherein said gene is linked to a promoter comprising any of the hexamers as recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of enablement is not commensurate with the enablement provided in regard to the large number of genes encompassed by the claims and coryneform bacteria comprising said genes. As indicated above, the specification discloses the mutation of coryneform bacterium promoters of the glutamate dehydrogenase, citrate synthase, isocitrate dehydrogenase, pyruvate dehydrogenase and arginosuccinate dehydrogenase genes, however, there is no disclosure of (1)

other genes involved in the biosynthesis of glutamic acid from other organisms, (2) the promoters of other genes involved in the biosynthesis of glutamic acid from other organisms comprising the recited hexamers, or (3) the critical structural elements which should be present in a polypeptide encoding an enzyme involved in glutamic acid biosynthesis. The state of the art, as evidenced by the teachings of Bork (Genome Research, 10:398-400, 2000), Broun et al. (Science 282:1315-1317, 1998), Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995), clearly teaches the unpredictability of isolating genes encoding similar enzymes by sequence homology. Since it is the amino acid structure what determines a protein's function, one of skill in the art would require some knowledge or guidance as to how structure is related to function in order to isolate the claimed genes. It is also noted that while the specification teaches that the coryneform bacterium promoters having the hexamers recited affect the expression of coryneform bacterium glutamate dehydrogenase, citrate synthase, isocitrate dehydrogenase, pyruvate dehydrogenase and arginosuccinate dehydrogenase, there is no disclosure of other mutated promoters comprising the recited hexamers having the same effect on the expression of similar enzymes in other organisms. As such, it is unclear if the expression of genes from other organisms linked to promoters comprising the hexamers recited would result in increased production of glutamic acid. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to display the desired enzymatic function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to isolate the claimed genes and their corresponding wild-type promoters as well as determining

if the claimed genes linked to promoters comprising the hexamers recited would also result in increased enzyme production or increased glutamic acid synthesis. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Baggio et al. (GenEMBL accession number BTU82241, January 11, 1997). Baggio et al. discloses the nucleotide sequence of a glutamate dehydrogenase from *Bacteroides thetaiotaomicron* which comprises the sequence TTGACA (positions 233-238) within the promoter region before the coding sequence, which starts at position 301 (see alignments already provided in Paper No. 10). Since claim 12 is directed to any gene encoding any enzyme involved in the biosynthesis of glutamic acid wherein said gene is linked to a promoter comprising any of the following hexamers: CGGTCA, TTGTCA, TTGACA, TTGCCA, or TATAAT, Baggio et al. anticipates claim 12 as written. See claim interpretation in claim rejections under 35 USC 112, second paragraph.

23. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Teller et al. (GenEMBL accession number CLOSGDHG, June 30, 1993). Teller et al. discloses the nucleotide sequence of a glutamate dehydrogenase from *C. symbiosum* comprising the sequence TATAAT (positions 34-39) within the promoter region before the coding sequence, which starts

at position 204 (see alignments already provided in Paper No. 10). Since claim 12 is directed to any gene encoding any enzyme involved in the biosynthesis of glutamic acid wherein said gene is linked to a promoter comprising any of the following hexamers: CGGTCA, TTGTCA, TTGACA, TTGCCA, or TATAAT, Teller et al. anticipates claim 12 as written. See claim interpretation in claim rejections under 35 USC 112, second paragraph.

Conclusion

24. No claim is in condition for allowance.

25. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

26. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
February 6, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600